Options for Once-Daily Dosing of Antiretrovirals / April 2006

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Introduction

The efficacy of antiretroviral therapy is influenced by many factors, including medication potency, pharmacokinetic features, drug interactions, adverse effects, and viral resistance. However, in initial treatment, drug adherence is the single most important factor for successful antiretroviral therapy. If complex dosing schedules present significant barriers to close adherence, simplified regimens consisting of once-daily antiretroviral therapy may increase adherence. Despite these advantages, there are potential risks associated with once-daily regimens. Trough drug levels may be marginal and missed doses may result in long periods of drug exposure that are inadequate for maintaining viral suppression.

Options for effective once-daily treatment are increasing. Ten antiretroviral agents or combinations have been approved by the U.S. Food and Drug Administration (FDA) for once-daily dosing and are currently available in the United States. These are the nucleoside or nucleotide analogues abacavir, didanosine, emtricitabine, lamivudine, and tenofovir; the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz; the protease inhibitor (PI) atazanavir; and the ritonavir-boosted PI combinations atazanavir/ritonavir, fosamprenavir/ritonavir, and lopinavir/ritonavir. Studies of certain other currently available medications suggest that they also may be administered successfully on a once-daily basis (see Table 2). Coformulations of antiretroviral medications reduce the number of pills required for a treatment regimen and further simplify dosing. Fixed dose combinations (FDCs) of abacavir + lamivudine and of emtricitabine + tenofovir are available and an FDC of emtricitabine + tenofovir + efavirenz is anticipated soon, in a one pill per day formulation.

Many of these once-daily medications have been studied in combination with twice-daily drugs, but have not been studied as components of an entirely once-daily regimen. The importance of carefully designed clinical trials to test once-daily regimens is highlighted by the unanticipated poor outcomes of several regimens (eg, efavirenz + didanosine + tenofovir as well as several triple-nucleoside combinations) and by unexpected drug interactions between certain antiretrovirals (eg, tenofovir and atazanavir).

To date, few efficacy studies of once-daily antiretroviral combinations have been conducted. Of the existing studies, most are small and nonrandomized and, therefore, must be interpreted with caution. The regimens most thoroughly studied contain the NNRTI efavirenz in combination with abacavir, didanosine, or tenofovir plus lamivudine or emtricitabine; these appear to be potent and durable in previously untreated patients. Few studies have examined once-daily regimens containing PIs, and none of these has included the newer PIs that are FDA approved for once-daily dosing: atazanavir and fosamprenavir. Two triple nucleoside regimens, abacavir + lamivudine + tenofovir and didanosine + lamivudine + tenofovir, have shown high rates of virologic failure and should be avoided. Further studies of once-daily treatments are in progress and will be important in determining the efficacy and tolerability of particular combinations.

Two additional agents, stavudine (extended-release formulation and the combination of amprenavir + ritonavir, were FDA approved but are not available.

Table 1: Potential Once-Daily Antiretroviral Combinations

The combinations indicated below (2 NRTIs + 1 NNRTI or PI) are anticipated to be effective in initial therapy for the treatment of HIV infection in adult patients. Please note that some of these combinations have not been studied in clinical trials.

NRTI combinations	+	NNRTI or PI
Abacavir + lamivudine *or* **emtricitabine** **Didanosine + lamivudine** *or* **emtricitabine** **Tenofovir + lamivudine** *or* **emtricitabine**¤ **Didanosine + tenofovir** * ¤	+	**Efavirenz** * **Nevirapine** * **Atazanavir** ¤ **Atazanavir/ritonavir** **Fosamprenavir/ritonavir** **Indinavir/ritonavir** **Lopinavir/ritonavir**

* Didanosine + tenofovir should not be used with efavirenz or nevirapine because of high rates of virologic failure. In addition the combination of didanosine + tenofovir has been associated with inferior improvement in CD4 cell counts

¤ Tenofovir cannot be used with unboosted atazanavir.

Table 2: Potential Once-Daily Antiretroviral Medications

Medication	Dosage	Notes
Nucleoside/Nucleotide Analogues (NRTIs)		
Abacavir	600 mg QD	• FDA approved for once-daily dosing. • Available in coformulation with lamivudine (Epzicom). • PK and clinical data support once-daily dosing. • Rates of hypersensitivity may be somewhat higher in once-daily groups. • Triple nucleoside regimen of abacavir + lamivudine + tenofovir showed high rates of virologic failure.
Didanosine, enteric-coated (Videx EC)	400 mg QD (wt >=60 kg) 250 mg QD (wt <60 kg)	• FDA approved for once-daily dosing. • PK and clinical data support once-daily administration. • To be taken on an empty stomach unless coadministered with tenofovir. • Dosage reduction recommended if taken concomitantly with tenofovir. • Combination of didanosine + tenofovir associated with inferior improvement in CD4 cell counts. • High rate of early virologic failure seen with didanosine + lamivudine in combination with efavirenz or nevirapine; also with triple nucleoside regimen of didanosine + tenofovir + lamivudine.
Emtricitabine	200 mg QD	• FDA approved for once-daily dosing. • PK and clinical data support once-daily administration. • Available in coformulation with tenofovir (Truvada). • Activity against hepatitis B virus.
Lamivudine	300 mg QD	• FDA approved for once-daily dosing. • PK and clinical data support once-daily administration. • Available in coformulation with abacavir (Epzicom). • High rate of early virologic failure seen with didanosine + lamivudine in combination with efavirenz or nevirapine; also with triple nucleoside regimen of didanosine + tenofovir + lamivudine. • Activity against hepatitis B virus.
Tenofovir	300 mg QD	• FDA approved for once-daily dosing. • Available in coformulation with emtriticine (Truvada). • PK and clinical data support once-daily administration. • PK interaction with didanosine; reduction in didanosine dosage may be required when tenofovir and didanosine are coadministered. • PK interaction with atazanavir; boosting of atazanavir levels with ritonavir may be required when tenofovir and atazanavir are coadministered. • Combination of didanosine + tenofovir associate with inferior improvement in CD4 cell counts. • High rate of early virologic failure seen with didanosine + tenofovir in combination with efavirenz or nevirapine; also with triple nucleoside regimen of didanosine + tenofovir + lamivudine. • Activity against hepatitis B virus.
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz	600 mg QHS	• FDA approved for once-daily dosing. • High rate of early virologic failure seen with didanosine + tenofovir + efavirenz. • PK and clinical data support once-daily administration. • If used concurrently with protease inhibitor, protease inhibitor may require dosage adjustment.
Nevirapine	400 mg QD	• Not FDA approved for once-daily dosing. • PK and clinical data support once-daily administration. • In one RCT, comparable efficacy between nevirapine BID and QD, and between nevirapine QD and efavirenz. • If used concurrently with protease inhibitor, protease inhibitor may require dosage adjustment. • High rate of early virologic failure seen with didanosine + tenofovir + nevirapine. • Should not be initiated in women with CD4 >250 cells/µL or men with CD4 >400 cells/µL.

Potential Once-Daily Antiretrovirals Medications *cont.*

Medication	Dosage	Notes
Protease Inhibitors (PIs)		
Atazanavir	400 mg QD	• FDA approved for once-daily dosing in antiretroviral-naive patients. • PK and clinical data support once-daily dosing. • Ritonavir-boosted atazanavir is recommended in antiretroviral-experienced patients. • Coadministration with tenofovir or an NNRTI may lower serum atazanavir levels; boosting with ritonavir is recommended.
Atazanavir + ritonavir	ATV 300 mg QD + RTV 100 mg QD	• FDA approved for once-daily dosing in treatment-experienced patients. • PK and clinical data support once-daily dosing.
Atazanavir + saquinavir	SQV 1,200 mg QD + ATV 400 mg QD SQV 1,200 mg QD + ATV 600 mg QD	• This combination is not FDA approved. • Limited data, 2 clinical efficacy studies. In treatment-experienced patients, less effective than lopinavir-ritonavir BID or atazanavir + ritonavir QD. • May achieve therapeutic levels of both PIs. • Coadministration with an NNRTI may lower serum saquinavir and atazanavir levels; dosage adjustment may be necessary.
Fosamprenavir + ritonavir	FPV 1,400 mg QD + RTV 200 QD	• FDA approved for once-daily dosing. • QD dosing is not recommended for PI-experienced patients (BID dosing appears to be more effective).
Indinavir + ritonavir	Various combinations studied (mg IDV/mg RTV QD): 1,200/400 1,200/100 1,200/200 1,000/100 800/200	• Not FDA approved for once-daily dosing. • Data are limited and are primarily from PK studies and small noncomparative studies. • Large interpatient variability in serum indinavir levels. • Insufficient data to assess clinical efficacy. • Coadministration with an NNRTI may lower serum indinavir levels; dosage adjustment may be necessary.
Lopinavir + ritonavir (Kaletra)	LPV 800 mg + RTV 200 mg QD	• FDA approved for once-daily dosing in treatment-naive patients. • Limited PK and clinical data. • Large interpatient variability in trough lopinavir levels. • Coadministration with NNRTI may lower serum lopinavir levels; dosage adjustment has not been defined, coadministration with NNRTI should be avoided at present. • Increased gastrointestinal adverse effects with once-daily dosing.
Saquinavir + ritonavir	SQV 1,600 mg QD + RTV 100 mg QD	• Not FDA approved for once-daily dosing. • PK and clinical data support once-daily administration. • In one RCT, less efficacious than efavirenz-based regimen; higher rate of adverse effects. • Large interpatient variability in saquinavir levels. • Gastrointestinal adverse effects appear to be less frequent with hard-gelatin capsule formulation. • Large pill burden if hard-gel formulation is used. No data on QD dosing of tablet formulation. • Coadministration with an NNRTI may lower serum saquinavir levels; dosage adjustment may be necessary.

Abbreviations

AUC = area under the curve
BID = twice daily
Cmax = maximal plasma concentration
FDA = U.S. Food and Drug Administration
PK = pharmacokinetics
QD = once daily
QHS = at bedtime
RCT = randomized controlled trial
wt = body weight

Antiretroviral abbreviations

ATV = atazanavir
FPV = fosamprenavir
IDV = indinavir
LPV = lopinavir
NFV = nelfinavir
RTV = ritonavir
SQV = saquinavir